2018 Current Fiscal Year Report: Drug Safety and Risk Management Advisory Committee

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1. Department or Agency	2. Fiscal Year
Department of Health and Human Services	2018

3. Committee or Subcommittee	3b. GSA Committee No.
Drug Safety and Risk Management Advisory Committee	847

4. Is this New During Fiscal Year?	5. Current Charter	6. Expected Renewal Date	7. Expected Term Date
No	05/31/2018	05/31/2020	

8a. Was Terminated During FiscalYear?	8b. Specific Termination Authority	8c. Actual Term Date
No		

9. Agency Recommendation for Next FiscalYear	10a. Legislation Req to Terminate?	10b. Legislation Pending?
Continue	Not Applicable	Not Applicable

11. Establishment Authority Authorized by Law

12. Specific Establishment Authority	13. Effective Date	14. Commitee Type	14c. Presidential?
21 U.S.C. 394	11/28/1990	Continuing	No

15. Description of Committee Scientific Technical Program Advisory Board

16a. Total Number of Reports	No Reports for this FiscalYear

17a. Open 1 **17b. Closed** 0 **17c. Partially Closed** 0 **Other Activities** 0 **17d. Total** 1

Meetings and Dates

Purpose	Start	End
The DSaRM met jointly with the Anesthetic and Analgesic Drug Products Advisory Committee to discuss results from assessments of the transmucosal immediate-release fentanyl (TIRF) medicines' risk evaluation and mitigation strategy (REMS), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency will seek the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system. The Agency will also seek the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met. Comments from the public can be submitted to the docket (see PUBLIC PARTICIPATION INFORMATION) on a broad evaluation of the TIRF REMS and whether any aspect of the TIRF REMS should be modified as well as any proposed modifications.	08/03/2018	08/03/2018

Number of Committee Meetings Listed: 1

	Current FY	Next FY
18a(1). Personnel Pmts to Non-Federal Members	$21,477.00	$52,497.00

18a(2). Personnel Pmts to Federal Members	$0.00	$0.00
18a(3). Personnel Pmts to Federal Staff	$172,271.00	$174,886.00
18a(4). Personnel Pmts to Non-Member Consultants	$16,239.00	$16,405.00
18b(1). Travel and Per Diem to Non-Federal Members	$32,211.00	$75,744.00
18b(2). Travel and Per Diem to Federal Members	$0.00	$0.00
18b(3). Travel and Per Diem to Federal Staff	$0.00	$0.00
18b(4). Travel and Per Diem to Non-member Consultants	$23,219.00	$18,895.00
18c. Other(rents,user charges, graphics, printing, mail, etc.)	$58,529.00	$59,340.00
18d. Total	$323,946.00	$397,767.00
19. Federal Staff Support Years (FTE)	1.10	1.10

20a. How does the Committee accomplish its purpose?

The Committee advises the Commissioner of Food and Drugs on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the Food and Drug Administration has regulatory responsibility. The committee also advises the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regards to safety, efficacy, and abuse potential of drugs or other substances, and recommends actions to be taken by the Department of Health and Human Sevices with regard to the maketing, investigation, and control of such drugs or other substances.

20b. How does the Committee balance its membership?

Members are authorities in the fields of risk communication, risk management, drug safety, medical, behavioral, and biological sciences as they apply to risk management, and drug abuse. The Committee includes one technically qualified voting member who is identified with consumer interests. The Committee may include one non-voting member identified with industry interests.

20c. How frequent and relevant are the Committee Meetings?

In FY-18, the committee held seven (7) meeting. At six (6) of these meetings, the Drug Safety and Risk Management Advisory Committee, met in joint session with other committees but was not the lead committee. See the Agency Recommendations, Remarks section for a list of joint meetings in which the committee was not the lead committee. On October 31, 2017, a meeting was held jointly with the Psychopharmacologic Drugs Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks section. On November 1, 2017, a meeting was held jointly with the Psychopharmacologic Drugs Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks

section. On February 14, 2018, a meeting was held jointly with the Anesthetic and Analgesic Drug Products Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks section. On April 24-25, 2018, a meeting was held jointly with the Arthritis Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks section. On May 22, 2018, a meeting was held jointly with the Anesthetic and Analgesic Drug Products Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks section. On June 26, 2018, a meeting was held jointly with the Anesthetic and Analgesic Drug Products Advisory Committee. Further information regarding this meeting is provided in the Recommendation Remarks section. On August 3, 2018, the Drug Safety and Risk Management Advisory Committee met jointly with the Anesthetic and Analgesic Drug Products Advisory Committee to discuss results from assessments of the transmucosal immediate-release fentanyl (TIRF) medicines' risk evaluation and mitigation strategy (REMS), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency sought the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system. The Agency will also sought the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. It is expected that the committee will meet four to six times in FY-19.

20d. Why can't the advice or information this committee provides be obtained elsewhere?

Members of the Committee are drawn from academia, research and/or clinical practice. Their advice and input lends credibility to regulatory decisions made and helps those decisions stand up to intense public scrutiny. The alternate means of obtaining this advice would be to hire large numbers of scientists on a full time basis at a great expense to the government.

20e. Why is it necessary to close and/or partially closed committee meetings?

During FY-18, the committee held one (1) partially closed meeting jointly with another committee but was not the lead committee. On June 26, 2018, from 8 a.m. to 9:30 a.m.,

the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee was closed to permit discussion and review of trade secret and/or confidential commercial information (5 U.S.C. 552b(c)(4)). During this session, the committees discussed the drug development program of an investigational opioid formulation with properties designed to deter abuse.

21. Remarks

In FY-18, the committee held seven (7) meeting. At six (6) of these meetings, the Drug Safety and Risk Management Advisory Committee, met in joint session with other committees but was not the lead committee. On October 31, 2017, the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to discuss new drug application (NDA) 209819, Sublocade (buprenorphine subcutaneous injection), submitted by Indivior Pharmaceuticals, Inc., for treatment of opioid dependence. Overall, the majority of the committee (18 to 1) agreed that the benefit and safety profile of buprenorphine was favorable for approval. The committee member voting “No”, expressed concerns over need for more data for safety. Regarding safety, the majority of the committee members (13 to 6) agreed that the safety data sufficiently supported the use of the proposed RBP 300 mg/300 mg dose regimen, even though the steady-state plasma exposures associated with RBP-6000 300 mg exceed those associated with the highest labeled dose of the reference product, Subutex. Those voting “Yes”, stated that it is necessary in clinical practice to go up on the dose of buprenorphine for effectiveness; the higher dose is needed for some patients with more severe opioid use disorders. Those committee members voting “No”, expressed concerns that they were unconvinced completely about the higher dose's added efficacy; they need to see more clinical safety data for the highest dose; and more toxicology studies are warranted. Most the committee members agreed that both the RBP-6000 300/300 mg and 300/100 mg regimen are efficacious. Committee members stated they mostly see no significant difference in the doses with respect to efficacy given that there is no good evidence against it. The members further stated that the higher doses should include liver function monitoring. Most the committee members agreed with the need for the FDA proposed addition to the applicant's proposed REMS to include a one-time certification of health care settings that order and dispense RBP-6000 to put systems in place from being dispensed directly to the patient. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. On November 1, 2017, the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to discuss new drug application (NDA) 210136, buprenorphine subcutaneous injection, submitted by Braeburn Pharmaceuticals, Inc., for treatment of opioid dependence. The majority of the committee members (17 members) recommended approval for some of the proposed doses. The

committee members voting “C” (3 members) expressed concerns over the trial design being problematic, and limited clinical data. The majority of the committee members (17 members) voted that the data from the clinical trial, taken together with the blockade study, provide substantial evidence of effectiveness of CAM2038 weekly and monthly formulations for the treatment of opioid use disorder in patients who are newly initiating buprenorphine treatment for some of the doses. Most of the committee members agreed that unsafe side effects were not observed with CAM2038. A few members commented that the clinical trial design mimics real world practice and is reflective of an effectiveness rather than efficacy trial, which should predict its success in treating opioid use disorders. However, other members disagreed and commented that the inherent design of the clinical trial, which did not allow for the collection of highly controlled data to predict the safety and efficacy of the CAM2038 doses investigated, was disappointing and a drawback. The majority of the committee members agreed and supported the need for the FDA's proposed addition to the REMS to include a one-time certification of health care settings that order and dispense CAM2038 to put systems in place from being dispensed directly to the patient. Some members commented that it may be too difficult to implement the REMS from a policy standpoint because of differences in State laws. The members also noted that the need for community pharmacists to be aware of patients use of CAM2038 via sharing of medication lists. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. On, February 14, 2018, the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to discuss new drug application (NDA) 209257, proposed tradename, HYDEXOR, a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees discussed the abuse potential of this non-abuse-deterrent product and whether it should be approved. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. On February 14, 2018, the Anesthetic and Analgesic Drug Products Advisory Committee met jointly with the Drug Safety and Risk Management Advisory Committee to discuss new drug application (NDA) 209257, proposed tradename, HYDEXOR, a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the shortterm management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees were also asked to discuss the abuse potential of this non-abuse-deterrent product and whether it should be approved. The majority of the committee (19 to 2) agreed that Hydexor should not be approved. Some of the committee members who voted “No” stated that their vote was based on the lack of dosing flexibility and that the

ramifications of the risks associated with Hydexor did not outweigh its benefit. Overall, the majority of the committee agreed that Hydexor poses greater risks than currently marketed hydrocodone-acetaminophen products. Some committee members added that an antiemetic may not be needed for every dose of analgesic, and that a fixed-dose combination of Hydexor would expose patients to unnecessary side effects of promethazine when it is not needed. Other committee members agreed that the applicant's proposed risk mitigation strategies are not convincing. One committee member who voted "Yes" viewed Hydexor as another opioid option and noted that its risks are no greater than what is currently on the market. Additionally, this member noted that that the population receiving Hydexor would be those who were prone to OINV and that the medication would be taken as needed. The other committee member who voted "Yes" stated that the overall benefits outweighed the risks but also suggested that toxicity data of promethazine when patients took more than six pills a day is needed. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. On April 24-25, 2018, the Arthritis Advisory Committee met jointly with the Drug Safety and Risk Management Advisory Committee to discuss supplemental new drug application (sNDA) 20998 for CELEBREX (celecoxib) capsules submitted by Pfizer, Inc., which includes the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) trial, a cardiovascular outcomes randomized controlled trial that compared celecoxib to ibuprofen and naproxen, and determine whether the findings of the trial change FDA's current understanding of the safety of these three NSAIDs. In order to interpret some of the PRECISION findings, the committees also considered the clinical implications of the drug interactions between each of these three NSAIDs and aspirin in patients taking aspirin for secondary prevention of cardiovascular disease. The majority of the committee (12 members) agreed that the Drug Facts label should include a warning regarding the interaction between aspirin and naproxen. These members mentioned the need for consistency between the OTC Drug Facts label of naproxen and that of ibuprofen. The majority of the committee members (17 members) also agreed that there should be no change to the current ibuprofen Drug Facts label. These members noted that there was no new information or data presented to warrant a change to the current label. Agency Action: The Agency is currently reviewing all recommendations that were made during the meeting. On May 22, 2018, the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to discuss new drug application (NDA) 209588, for buprenorphine sublingual spray, submitted by INSYS Development Company, Inc., for the treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committees were also asked to discuss whether this product should be approved. The majority of the committee (18 to 1) voted "No", that the benefits of Buvaya do not outweigh the risks for the indication, "the management of pain severe

enough to require an opioid analgesic and for which alternative treatments are inadequate," supporting approval of Buvaya. These members also agreed that although a commendable effort was made by the applicant to introduce an innovative product that may be less likely to be abused than some schedule II opioid analgesics, the factors contributing to their vote were the late onset of analgesia, and high rate of adverse events (primarily hypoxia). The committee member who voted "Yes" explained that the low abuse potential and the lack of alternative treatments available in the market were factors considered in the vote. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. On June 26, 2018, the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to discuss new drug application 022324, oxycodone extended-release capsules, submitted by Pain Therapeutics, with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties. The committees were also asked to discuss whether the data submitted by the Applicant are sufficient to support labeling of the product with the properties expected to deter abuse. The majority of the panel members (14 to 3) voted "No", that the efficacy, safety and risk-benefit profile of Remoxy ER do not support the approval of this application. The committee members largely agreed that the public health risks of approving this reformulation of oxycodone does not outweigh its benefits. Other comments included that approving Remoxy ER with an abuse deterrent label may create a false sense of safety for this formulation and that the benefits of its nasal deterrence properties are not enough to justify approval with abuse deterrent labeling. Panelists voting "No" largely agreed that Remoxy ER did not demonstrate enough abuse deterrent properties via the oral and IV routes of administration. Of the committee members who voted "Yes," the key comments were that the Applicant had met the standard for safety and efficacy and also met the criteria for abuse deterrence via the nasal and IV routes. Agency Action: The Agency is still reviewing all recommendations that were made at the meeting. This committee is expected to meet 5-6 times in FY-19.

Designated Federal Officer

Philip A. Bautista Designated Federal Officer

Committee Members	Start	End	Occupation	Member Designation
Besco, Kelly	08/26/2015	05/31/2019	Health-System Medication Safety Coordinator, Ohio-Health Pharmacy Services	Special Government Employee (SGE) Member
Boudreau, Denise	06/01/2017	05/31/2021	Senior Scientific Investigator, Kaiser Permanente Health Research Institute	Special Government Employee (SGE) Member

Choudhry, Niteesh	05/14/2015	05/31/2018	Professor, Harvard Medical School; Associate Physician, Brigham and Women's Hospital	Special Government Employee (SGE) Member
Griffin, Marie	06/01/2018	05/31/2022	Professor, Health Policy and Medicine, Vanderbilt University Medical Center	Special Government Employee (SGE) Member
Habel, Laurel	06/01/2017	05/31/2021	Associate Director, Cancer Research Division of Research, Kaiser Permanente Northern California	Special Government Employee (SGE) Member
Hernandez-Diaz, Sonia	06/01/2018	05/31/2022	Professor of Epidemiology, Harvard T.H. Chan School of Public Health	Special Government Employee (SGE) Member
Kulldorff, Martin	06/01/2018	05/31/2022	Professor of Medicine and Biostatistician, Harvard Medical School and Brigham & Women's Hospital	Special Government Employee (SGE) Member
Meisel, Steven	06/01/2017	05/31/2021	System Director of Medication Safety, Fairview Health Services/Healtheast Care System	Special Government Employee (SGE) Member
Robotti, Suzanne	01/19/2017	05/31/2020	Executive Director, DES Action USA	Representative Member
Ruha, Anne-Michelle	09/19/2016	05/31/2020	Vice-Chief, Department of Medical Toxicology, Banner University Medical Center	Special Government Employee (SGE) Member
Scarazzini, Linda	03/31/2016	10/31/2019	Vice President, Pharmacovigilace and Drug Safety, AbbVie	Representative Member
Schmid, Christopher	05/14/2015	05/31/2018	Professor of Biostatistics, Center for Evidence Based Medicine, Department of Biostatistics, Brown University of Public Health	Special Government Employee (SGE) Member
Setoguchi, Soko	06/01/2017	05/31/2021	Associate Professor of Medicine and Epidemiology, Rutgers University	Special Government Employee (SGE) Member
Warholak, Terri	09/19/2016	05/31/2020	Professor and Assistant Dean, Academic Affairs and Assessment, University of Arizona College of Pharmacy	Special Government Employee (SGE) Member
Winterstein, Almut	05/14/2015	05/31/2018	Professor and Crisafi Chair, Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida	Special Government Employee (SGE) Member

Number of Committee Members Listed: 15

Narrative Description

FDA’s strategic priorities in responding to the public health challenges of the 21st century are to advance regulatory science and innovation; strengthen the safety and integrity of the global supply chain; strengthen compliance and enforcement activities to support public health; expand efforts to meet the needs of special populations; advance medical countermeasures and emergency preparedness; advance food safety and nutrition; promote public health by advancing the safety and effectiveness of medical products; establish an effective tobacco regulation, prevention, and control program; and manage for organizational excellence and accountability. The Drug Safety and Risk Management Advisory Committee supports FDA's strategic priorities by reviewing and evaluating available data on risk management, risk communication, and quantitative evaluation of

spontaneous reports for drugs for human use and for any other product for which the Food and Drug Administration has regulatory responsibility and making appropriate recommendations to the Commissioner of Food and Drugs. The Committee also advises the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances, and recommends actions to be taken by the Department of Health and Human Services with regard to the marketing, investigation, and control of such drugs or other substances. This supports the development of safe and effective new medical technologies, and advances the status of the Agency as a science-based and science-led regulatory agency, providing global leadership in the protection of public health.

What are the most significant program outcomes associated with this committee?

	Checked if Applies
Improvements to health or safety	✓
Trust in government	✓
Major policy changes	✓
Advance in scientific research	✓
Effective grant making	
Improved service delivery	
Increased customer satisfaction	✓
Implementation of laws or regulatory requirements	✓
Other	

Outcome Comments

N/A

What are the cost savings associated with this committee?

	Checked if Applies
None	
Unable to Determine	✓
Under $100,000	
$100,000 - $500,000	
$500,001 - $1,000,000	
$1,000,001 - $5,000,000	
$5,000,001 - $10,000,000	
Over $10,000,000	
Cost Savings Other	

Cost Savings Comments

The utilization of the Drug Safety and Risk Management Drugs Advisory Committee enabled the Agency to obtain required and frequently scarce professional services from medical and scientific experts not otherwise available to the Agency; and to obtain the services of these experts only on an as needed basis rather than on a full time basis. The service of the Committee resulted in advice for the improvement of the public health, for which it is difficult to assign a financial value.

What is the approximate Number of recommendations produced by this committee for the life of the committee?

56

Number of Recommendations Comments

The committee made 56 recommendations from FY-03 through FY-18. See question 20a of the annual report for specific accomplishments.

What is the approximate Percentage of these recommendations that have been or will be Fully implemented by the agency?

79%

% of Recommendations Fully Implemented Comments

The function of an advisory committee is purely advisory in nature. Although the FDA most often accepts the recommendations from its committees, the advice is purely advisory in nature, and therefore, the Agency has the option of not implementing the advice.

What is the approximate Percentage of these recommendations that have been or will be Partially implemented by the agency?

9%

% of Recommendations Partially Implemented Comments

The function of an advisory committee is purely advisory in nature. Although the FDA most often accepts the recommendations from its committees, the advice is purely advisory in nature, and therefore, the Agency has the option of not implementing the advice.

Does the agency provide the committee with feedback regarding actions taken to implement recommendations or advice offered?

Yes ☑ No ☐ Not Applicable ☐

Agency Feedback Comments

It usually does. Product approval issues are first released to the sponsor. When appropriate, information is made available to the public. Actions related to guidance documents or other general matters issues are available publicly when implemented.

What other actions has the agency taken as a result of the committee's advice or recommendation?

	Checked if Applies
Reorganized Priorities	☑
Reallocated resources	☐
Issued new regulation	☑
Proposed legislation	☐
Approved grants or other payments	☐
Other	☑

Action Comments

FDA approves or chooses not to approve an investigational new medical product.

Is the Committee engaged in the review of applications for grants?

No

Grant Review Comments

N/A

How is access provided to the information for the Committee's documentation?

	Checked if Applies
Contact DFO	☑
Online Agency Web Site	☑
Online Committee Web Site	☑
Online GSA FACA Web Site	☑
Publications	☑
Other	☐

Access Comments

N/A